Self-Reported and Physiologic Reactions to Third BNT162b2 mRNA COVID-19 (Booster) Vaccine Dose

Merav Mofaz, Matan Yechezkel, Grace Guan, Margaret L. Brandeau,
Tal Patalon, Sivan Gazit, Dan Yamin,[1] Erez Shmueli[1]

Despite extensive technological advances in recent years, objective and continuous assessment of physiologic measures after vaccination is rarely performed. We conducted a prospective observational study to evaluate short-term self-reported and physiologic reactions to the booster BNT162b2 mRNA (Pfizer-BioNTech, https://www.pfizer.com) vaccine dose. A total of 1,609 participants were equipped with smartwatches and completed daily questionnaires through a dedicated mobile application. The extent of systemic reactions reported after the booster dose was similar to that of the second dose and considerably greater than that of the first dose. Analyses of objective heart rate and heart rate variability measures recorded by smartwatches further supported this finding. Subjective and objective reactions after the booster dose were more apparent in younger participants and in participants who did not have underlying medical conditions. Our findings further support the safety of the booster dose from subjective and objective perspectives and underscore the need for integrating wearables in clinical trials.

The severe acute respiratory syndrome coronavirus 2 Delta variant (also termed variant B.1.617.2) was discovered in October 2020 in India and was designated as a variant of concern by the World Health Organization in May 2021 (*1–3*). Since its discovery, it has spread worldwide and has rapidly become the most dominant variant in many countries (*4–7*). Although the BNT162b2 COVID-19 vaccine (Pfizer-BioNTech, https://www.pfizer.com) is highly effective against the Alpha variant (*8*), recent studies show that the

effectiveness of the Pfizer-BioNTech vaccines is notably lower against the Delta variant: 88% compared with 93.7% against the Alpha variant (*9–12*). Moreover, recent evidence shows that fully vaccinated persons infected with the virus can easily transmit it because their peak viral burden is similar to that observed for unvaccinated persons (*7,10*). In Israel, the Delta variant has accelerated coronavirus disease (COVID-19) infection and hospitalization; numbers doubled every 10 days during July 1–August 9, 2021 (*7,13*), despite the high coverage of the BNT162b2 vaccine in Israel during this period, which was >75% coverage with 2 Pfizer doses in the eligible population (persons ≥12 years of age) (*13*).

The rapid increase in hospitalizations associated with the Delta-driven COVID-19 resurgence and the imminent risk for hospital overcrowding led the Israeli government to initialize on July 30, 2021, an unparalleled, proactive, national third (booster) vaccine shot campaign, offering the BNT162b2 mRNA COVID-19 vaccine to persons >60 years of age. On August 13, 2021, the booster campaign was expanded to include persons >50 years of age and reached 63% third-dose coverage among the eligible population within only 26 days (*7,14–16*). Two weeks later, on August 29, 2021, the campaign was expanded to include all persons ≥16 years of age, requiring only that 5 months had passed since the receipt of the second dose. This effort reached 40% third-dose coverage among the eligible population <50 years of age within 16 days (*13,17*).

Limited information is available on the safety of a BNT162b2 third dose (*18,19*). Such a booster vaccine has yet to be authorized by the US Food and Drug Administration (FDA) for the general population (*20*). Although recent evidence shows that a third BNT162b2 dose for immunocompromised persons

Author affiliations: Tel Aviv University, Tel Aviv, Israel (M. Mofaz, M. Yechezkel, D. Yamin, E. Shmueli); Stanford University, Stanford, California, USA (G. Guan, M.L. Brandeau); Maccabi Healthcare Services, Tel Aviv (T. Patalon, S. Gazit); Massachusetts nstitute of Technology Media Laboratory, Cambridge Massachusetts, USA (E. Shmueli)

[1]These authors contributed equally to this article.

has a favorable safety profile (*19,21*), the safety of a third (booster) dose in the general population has not yet been fully established.

Clinical trial guidelines for assessing the safety of vaccines, including the FDA criteria (*22*), are primarily based on subjective, self-reported questionnaires. Despite the extensive advances in recent years, objective, continuous assessment of physiologic measures postvaccination is rarely performed. Two recent pioneering studies demonstrated the use of wearable devices to monitor short-term physiologic changes after the first and second doses of the BNT162b2 mRNA vaccine. The first study (*23*) used a chest-patch sensor to monitor changes in 13 different cardiovascular and hemodynamic vitals in a cohort of 160 persons up to 3 days postvaccination. The second study (*24*) used a consumer-grade smartwatch to evaluate changes in heart rate variability (HRV), resting heart rate, and respiration rate in a cohort of 19 persons. Both studies found major changes in several physiologic measures in the first days after vaccination.

We evaluated the short-term effects of a third BNT162b2 mRNA COVID-19 vaccine dose on self-reported and physiologic indicators on a relatively large sample. Specifically, we tested 2,912 participants; of these persons, 1,609 participants received >1 doses of the BNT162b2 vaccine after entering the study. Participants were equipped with Garmin (https://www.garmin.com) Vivosmart 4 smart fitness trackers and completed daily questionnaires by using a dedicated mobile application for 37 days, starting 7 days before vaccination. The mobile application collected daily self-reported questionnaires on local and systemic reactions, as well as various well-being indicators. The smartwatch continuously monitored several physiologic measures, including heart rate, HRV, and blood oxygen saturation level (SpO$_2$). Our analysis of comprehensive data for each participant examined the safety of a third (booster) vaccine dose from a subjective perspective (self-reported questionnaire) and an objective perspective (smartwatch data).

Materials and Methods

Study Design and Participants
The 2,912 participants (>18 years of age) in our study were recruited during November 1, 2020–September 15, 2021. The 1,609 participants who reported receipt of >1 of the 3 BNT162b2 mRNA COVID-19 vaccine shots after joining the study served as the base dataset for our analysis. All participants received the BNT162b2 mRNA vaccine. Specifically, of the 1,609 participants, during the study, 223 received their first dose, 351 their second dose, and 1,344 their third dose. Among these participants, 111 received both the second and third doses, 85 received both the first and third doses, and 80 received all 3 doses.

We used a professional survey company to recruit participants and ensure they followed through with the study requirements. Participant recruitment was performed by using advertisements on social media and word-of-mouth. Each participant provided informed consent by signing a form after receiving a comprehensive explanation on the study. Participants then completed a 1-time enrollment questionnaire, were equipped with Garmin Vivosmart 4 smartwatches, and installed 2 applications on their mobile phones: the PerMed application (*25*), which collected daily self-reported questionnaires, and an application that passively recorded the smartwatch data. Participants were asked to wear their smartwatches as much as possible. The survey company ensured that participants' questionnaires were completed daily, that their smartwatches were charged and properly worn, and that any technical problems with the mobile applications or smartwatch were resolved. Participants were monitored through the mobile application and smartwatches for 37 days, starting 7 days before vaccination.

We implemented several preventive measures to minimize attrition and churn (attrition rate) of participants and consequently improve the quality, continuity, and reliability of the collected data. First, each day, if by 7:00 PM participants had not yet completed the daily questionnaire, they received a reminder notification through the PerMed application. During the peak periods of COVID-19 vaccination in Israel, we increased the frequency of the reminders and adjusted their content. Second, we developed a dedicated dashboard that enabled the survey company to identify participants who continually neglected to complete the daily questionnaires or did not wear their smartwatch for a long period of time; these participants were contacted by the survey company (either by text messages or telephone calls) and were encouraged to better adhere to the study protocol. Third, to strengthen participants' engagement, a weekly personalized summary report was generated for each participant and was available inside the PerMed application. Similarly, we sent a monthly newsletter that contained recent findings from the study and useful tips regarding the smartwatch's capabilities to the participants.

PerMed Mobile Application

Participants used the PerMed mobile application (*25*) to fill out daily questionnaires. The questionnaire enabled participants to report various well-being indicators, including mood level (on a scale of 1 [awful] to 5 [excellent]), stress level (on a scale of 1 [very low] to 5 [very high]), sport activity duration (in minutes), and sleep quality (on a scale of 1 [awful] to 5 [excellent]). The questionnaire also collected data on clinical symptoms consistent with the local and systemic reactions observed in the BNT162b2 mRNA COVID-19 clinical trial (*26*), with an option to add other symptoms as free text (Appendix, https://wwwnc.cdc.gov/EID/article/28/7/21-2330-App1.pdf).

Smartwatch

Participants were equipped with Garmin Vivosmart 4 smart fitness trackers. Among other features, the smartwatch provides all-day heart rate and HRV and overnight SpO_2 tracking capabilities (*27*).

The optical wrist heart rate monitor of the smartwatch is designed to continuously monitor heart rate. The frequency at which heart rate is measured varies and might depend on the level of activity of the user: when the user starts an activity, the optical heart rate monitor's measurement frequency increases.

Because HRV is not easily accessible through Garmin's application programming interface, we use Garmin's stress level instead, which is calculated on the basis of HRV. Specifically, the device uses heart rate data to determine the interval between each heartbeat. The variable length of time between each heartbeat is regulated by the body's autonomic nervous system. Less variability between beats correlates with higher stress levels, whereas an increase in variability indicates less stress (*28*). A similar relationship between HRV and stress was also seen by Kim et al. (*29*) and Pereira et al. (*30*).

The pulse oximetry monitor of the smartwatch uses a combination of red and infrared lights with sensors on the back of the device to estimate the percentage of oxygenated blood (peripheral SpO_2%). This monitor is activated each day at a fixed time for 4 hours (the default is 2:00–6:00 AM). When we examined data collected in our study, we identified a heart rate sample approximately every 15 seconds, an HRV sample every 180 seconds, and an SpO_2 sample every 60 seconds.

Although the Garmin smartwatch provides state-of-the-art wrist monitoring, it is not a medical-grade device. Some readings might be inaccurate under certain circumstances, depending on factors such as the fit of the device and the type and intensity of the activity undertaken by a participant (*31–33*).

Statistical Analysis

We preprocessed questionnaire data by manually categorizing any self-reported symptom entered as free text. In addition, if participants completed the questionnaire >1 time in 1 day, we used the last entry from that day for the analysis. We preprocessed smartwatch data as follows. We computed the mean value of each hour of data. We then performed linear interpolation to impute missing hourly means and smoothed the data by calculating the 5-hour moving average.

For each participant, we defined the 7-day period before vaccination as the baseline period. We noted any clinical symptoms from the last questionnaire completed during the baseline period. Next, we calculated the percentage of participants who reported new systemic reactions in the 48 hours after vaccination. For each reaction, we used a β distribution to determine a 90% CI. To determine the statistical significance of differences between the first and third doses and between the second and third doses as reflected by the extent of reported reactions, we used a test for comparing proportions of 2 partially overlapping samples with unequal variance (*34*).

We also calculated the mean difference in well-being indicators between the postvaccination and baseline periods. Specifically, for each indicator, for each of the 3 days postvaccination and for each participant, we calculated the difference between that indicator's value and its corresponding value in the baseline period. We then calculated the mean value over all participants and the associated 90% CI.

To compare the changes in smartwatch physiologic indicators over the 7 days (168 hours) postvaccination with those of the baseline period, we performed the following steps. First, for each participant and each hour during the 7 days postvaccination, we calculated the difference between that hour's indicator value and that of the corresponding hour in the baseline period (keeping the same day of the week and same hour during the day). Then, we aggregated each hour's differences over all participants to calculate a mean difference and associated 90% CI, which is analogous to a 1-sided t-test a with significance level of 0.05. To determine the statistical significance of differences between the first and third doses and between the second and third doses as reflected by changes in smartwatch indicators during the 48 hours postvaccination, we used a test for comparing means of 2 partially overlapping samples with unequal variance (*35*).

We repeated our analyses for the third dose stratified by age groups (<50, 50–64, and >65 of age), sex, and underlying medical condition (present

versus not present) from a specified list (Table). To determine the statistical significance of differences between the groups in these analyses, we used a t-test for comparing the means of 2 independent samples with unequal variance.

Ethics Approval

Before participating in the study, all persons were advised, both orally and in writing, as to the nature of the study and provided written informed consent. The study was approved by the Maccabi Health Services Helsinki Institutional Review Board (protocol no. 0122–20-MHS).

Results

Of the 1,609 participants who received >1 dose of the BNT162b2 vaccine after joining the study, 854 (53.08%) were women and 755 (46.92%) men. Their ages were 18–88 years; median age was 52 years (Table). A total of 1,258 (78.19%) participants had a body mass index <30 kg/m², and 412 (25.61%) had >1 specific underlying medical condition (Table). The distributions of age and sex and underlying medical conditions were relatively invariable across the recipients of the first, second, and third doses (Table).

Our examination of self-reported reactions showed that the extent of systemic reactions reported after the third vaccine dose was similar to those reported after the second dose (p = 0.76) and considerably greater than those observed after the first dose (p<0.001) (Figure 1). Specifically, 60.4% (90% CI 57.9%–62.9%) of the participants did not report any new symptoms after receiving the third dose compared with 86.5% (90% CI 81.9%–91.0%) after the first dose and 63.6% (90% CI 59.1%–67.8%) after the second dose. Moreover, the most frequently reported types of reactions (fatigue, headache, muscle pain, fever, and chills) were similar after the second and third doses. These reactions decreased in nearly all participants within 3 days (Appendix Figure 8). These trends are consistent with those reported for the first and second dose BNT162b2 mRNA vaccine clinical trial (26).

For the self-reported well-being indicators (Figure 2), we found that during the first 2 days after the third vaccine dose, participants showed a major reduction in mood level (Figure 2, panel A), sport duration (Figure 2, panel C), and sleep quality (Figure 2, panel D) and a large increase in stress level (Figure 2, panel B) compared with baseline levels. These changes decreased on the third day postvaccination. A similar trend was observed after the second vaccine dose, except for the reported stress level, which remained below the baseline level during the second and third days postvaccination.

We observed similar trends when analyzing objective and continuous physiologic measurements collected by the smartwatch (Figure 3, https://wwwnc.cdc.gov/EID/article/28/7/21-2330-F3.htm; Appendix Figure 1). Specifically, we identified a considerable

Table. Characteristics of participants in study of self-reported and physiologic reactions to third BNT162b2 mRNA coronavirus disease (booster) vaccine dose*

Characteristic	All participants, n = 1,609	First dose, n = 223	Second dose, n = 351	Third dose, n = 1,344
Sex				
M	755 (46.92)	101 (45.29)	160 (45.58)	639 (47.54)
F	854 (53.08)	122 (54.71)	191 (54.42)	705 (52.46)
Age group, y				
18–29	226 (14.23)	14 (6.28)	39 (11.11)	189 (14.06)
30–39	272 (16.90)	11 (4.93)	53 (15.10)	219 (16.29)
40–49	177 (11.00)	15 (6.73)	42 (11.97)	138 (10.27)
50–59	420 (26.10)	64 (28.70)	87 (24.79)	375 (27.90)
60–69	358 (22.25)	70 (31.39)	75 (21.37)	308 (22.92)
>70	153 (9.51)	49 (21.97)	55 (15.67)	8.56 (115)
Body mass index, kg/m²				
<30.0	1,258 (78.19)	175 (78.48)	280 (79.77)	77.68 (1,044)
>30.0	330 (20.51)	41 (18.39)	60 (17.09)	288 (21.43)
Unspecified	21 (1.31)	7 (3.14)	11 (3.13)	12 (0.89)
Underlying medical condition				
Hypertension	228 (14.17)	20.63 (46)	15.95 (56)	14.43 (194)
Diabetes	139 (8.64)	13.00 (29)	7.98 (28)	8.41 (113)
Heart disease	77 (4.79)	7.17 (16)	4.56 (16)	4.99 (67)
Chronic lung disease	81 (5.03)	4.93 (11)	3.70 (13)	5.21 (70)
Immune suppression	13 (0.81)	1.35 (3)	0.85 (3)	0.89 (12)
Cancer	10 (0.62)	0.45 (1)	0.57 (2)	0.67 (9)
Renal failure	8 (0.50)	1.79 (4)	1.42 (5)	0.45 (6)
None of the above	1,180 (73.34)	64.57 (144)	72.08 (253)	73.21 (984)
Unspecified	17 (1.06)	1.35 (3)	2.85 (10)	0.52 (7)

*Values are no. (%). BNT162b2 vaccine, Pfizer-BioNTech (https://www.pfizer.com).

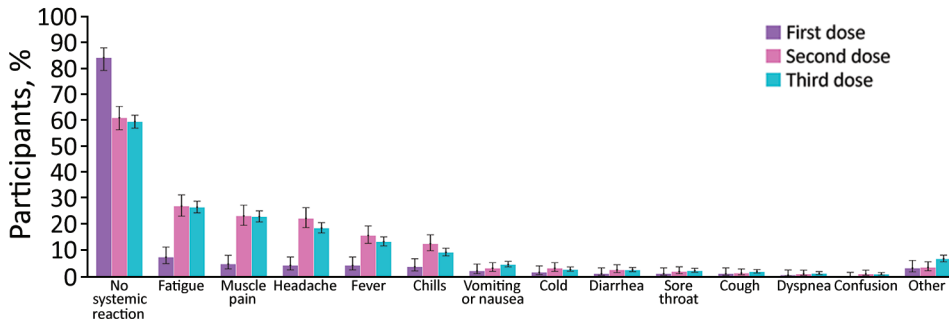**Figure 1.** Reactions reported by participants through a mobile application for self-reported and physiologic reactions to BNT162b2 (Pfizer, https://www.pfizer.com) mRNA coronavirus disease vaccine doses. Error bars indicate 90% CIs.

increase in heart rate (Figure 3, panels A–C) and the HRV-based stress indicators (Figure 3, panels D–F) during the first 48 hours after administration of the third dose. Measurements returned to baseline levels within 72 hours. In contrast, our analysis of SpO_2 suggests no apparent changes after vaccination compared with baseline levels (Figure 3, panels G–I), a result that is consistent with the results of Gepner et al. (*23*). The trends observed for the objective heart rate and HRV indicators were consistent with those of the subjective indicators: similar changes after the second and third doses (heart rate p = 0.86, HRV p = 0.54), and greater changes after the third dose than the first dose (heart rate p = 0.004, HRV p<0.001).

We also stratified our analyses of well-being and smartwatch physiologic indicators after the third vaccination by age group, sex, and a previous underlying medical condition (Figure 4; Appendix Figures 2–7). For all stratifications, trends were similar to those observed in the general population. We found considerable changes in the 2 days after vaccine administration that decreased almost entirely after 3 days. We

also found that participants ≥65 years of age reported fewer reactions (p<0.001) than did participants 50–65 years of age, who in turn reported even fewer reactions (p = 0.007) than did participants <50 years of age (Figure 4, panel A). In terms of the objective physiologic measures, participants ≥65 years of age showed milder changes in HRV than did participants 50–65 years of age (p = 0.075) and milder changes in heart rate (p = 0.02) than did participants <50 years of age (Figure 4, panel B).

Male participants reported fewer reactions (p<0.001) but did not show milder physiologic changes (heart rate p = 0.37, HRV p = 0.59) than female participants. Participants who had an underlying medical condition reported fewer reactions (p<0.001) and showed milder physiologic changes (heart rate p = 0.042, HRV p = 0.16), compared with participants who did not have an underlying medical condition. Of 9 participants who reported dyspnea, 4 (0.96% of their age group) were <50 years of age, 4 (0.93% of their age group) were 50–64 years of age, and 1 (0.65% of her age group) was ≥65 years of age. One participant
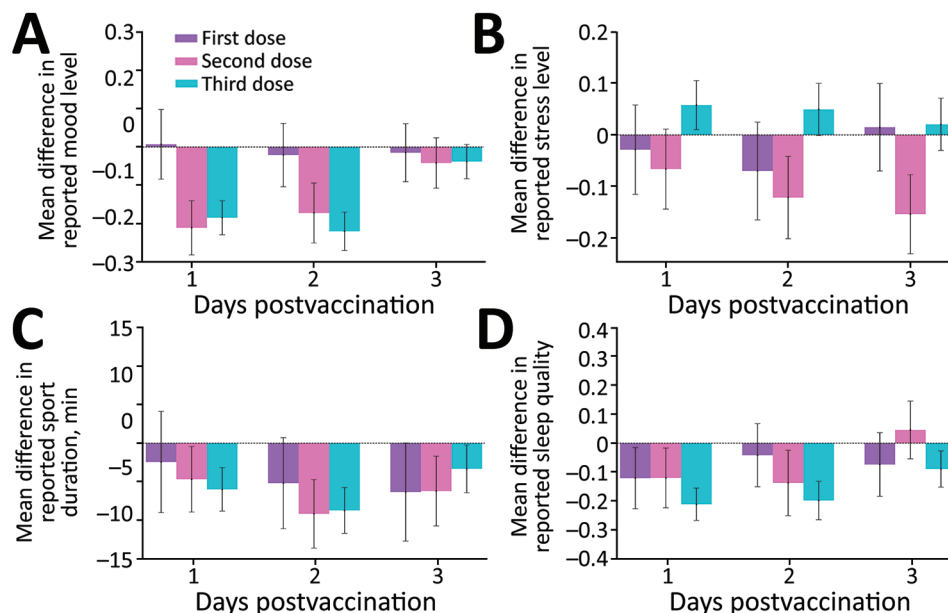

Figure 2. Changes in subjective well-being indicators reported by participants through a mobile application for self-reported and physiologic reactions to BNT162b2 (Pfizer, https://www.pfizer.com) mRNA coronavirus disease vaccine doses. Mean difference compared with baseline levels are shown for the well-being indicators of mood level (A), stress level (B), sport duration (C), and sleep quality (D). Mood level, stress level, and sleep quality were reported on a 1–5 Likert scale. Sport duration was measured in minutes. Error bars indicate 90% CIs. Horizontal dashed lines indicate no change compared with baseline levels.
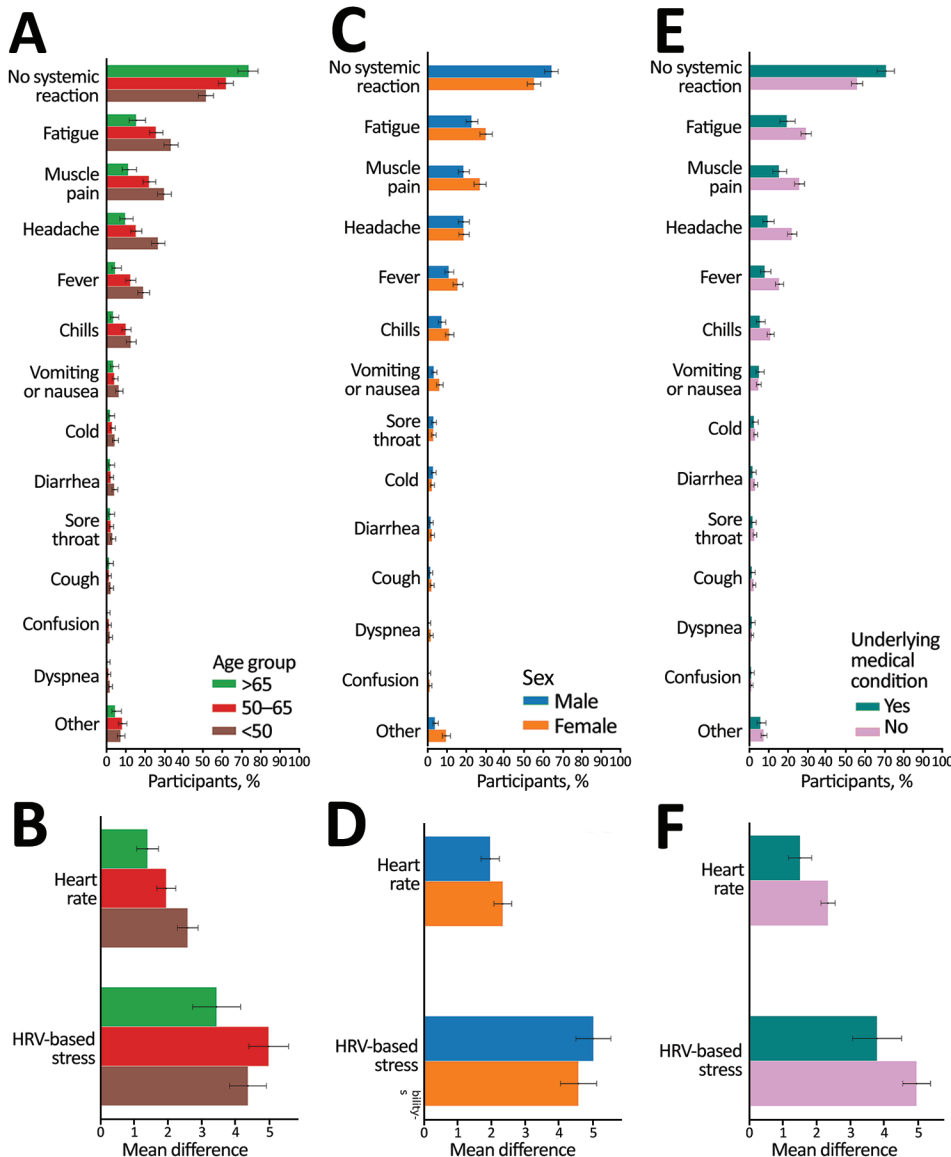
Figure 4. Self-reported and objective reactions following the third vaccine dose, stratified by age, sex, and underlying medical condition for self-reported and physiologic reactions to third BNT162b2 (Pfizer, https://www.pfizer.com) mRNA coronavirus disease vaccine doses. Reactions reported by participants through the mobile application (A, C, E) and objective heart rate and heart rate variability measured through a smartwatch (B, D, F) are shown, stratified by age (A, B), sex (C, D), and underlying medical condition (E, F). Bars indicate percentage of participants with a reported or recorded reaction; error bars indicate 90% CIs.

<50 years of age reported chest pain after vaccination. None of these participants had an underlying medical condition. These reactions (i.e., dyspnea and chest pain) disappeared 2–4 days after vaccination.

Discussion

Our key findings suggest that local and systemic reactions reported after the third (booster) vaccine dose administration are similar to those reported after the second dose and considerably greater than those observed after the first dose. Our analyses of self-reported well-being indicators and objective smartwatch physiologic indicators underscore these results. Furthermore, within 3 days from vaccination with the third dose, all measures returned to their baseline levels in all participants. We identified differences in subpopulations on the basis of sex, age, and underlying medical conditions after administration of the third vaccine dose. It has been suggested that reactions caused by the COVID-19 vaccine are a byproduct of a short burst of interferon type I generation concomitant with induction of an effective immune response (*36*). Interferon type I generation is substantially stronger in women than in men and stronger in younger and healthier persons than in older and less healthy persons. We found that participants <65 years of age, female participants, and participants without an underlying medical condition showed greater reactions in self-reported local and systemic reactions and well-being indicators, as well as in objective physiologic measurements recorded by the smartwatch. Our results are also consistent with the

results of a previous study that found similar trends after the first and second doses (*37*).

Clinical trials have not yet used the comprehensive physiologic measures generated by wearable devices, such as smartwatches. Currently, the FDA and European Medicines Agency evaluate the safety of and create guidelines for newly developed vaccines primarily on the basis of subjective, self-reported questionnaires (*22*,*38*). Much of the scientific literature discusses these self-reported side effects of COVID-19 vaccines. However, integrating wearable devices into clinical trials, alongside self-reported questionnaires, can provide more precise and rich data regarding the vaccines' effects on physiologic measures.

Our study's first limitation is that the 1,609 persons who comprised the base dataset of our analyses might not be representative of the vaccinated population in Israel or globally. Nevertheless, the changes observed in self-reported reactions and well-being indicators, as well as objective physiologic indicators recorded by the smartwatches, were statistically significant and consistent with each other. Moreover, the reaction types, frequency, and duration we observed for the first and second doses were similar to those observed in the BNT162b2 mRNA vaccine clinical trials (*26*). In addition, a clear pattern of returning to baseline levels was observed within 72 hours after vaccination in all examined measures. Although the sample size was limited, trends were consistent regardless of age group, sex, and underlying medical conditions.

Second, we did not explicitly control for the effects of the observational trial setting (e.g., participating in a trial, wearing a smartwatch, potential concerns regarding the vaccine). Any effects of the observational trial setting should, in principle, have similar effects on our analysis of each of the 3 vaccine doses. However, because we found no deviations in most measurements from baseline levels in the subset of participants who received their first dose, we believe the changes observed after the second and third doses arise from an actual reaction to the vaccine.

Third, the smartwatches used to obtain physiologic measurements are not medical-grade devices. Nevertheless, recent studies show a considerably accurate heart rate measurement in the previous versions of the smartwatch used in this study (*31*,*32*). In the same context, for some measures, such as SpO_2, the timing of measurement might be different across participants (e.g., if they changed their default settings). In both instances, it is useful to emphasize that our analyses focused on the change in measurements compared with their baseline values, rather than on their absolute values.

Fourth, all participants in our study received the BNT162b2 mRNA vaccine. Although our findings might not be directly generalized to other types of COVID-19 vaccines, we believe that applying our analyses on other vaccines is likely to yield qualitatively similar findings because of the similarities observed between different COVID-19 vaccines (*26*,*39*,*40*).

It would be useful to evaluate the effect of previous COVID-19 infection episodes on the results we obtained. However, although our data set contains some information on COVID-19 infections of participants during the time they spent in the study, it lacks information on infection episodes that occurred before they joined the study, making such analyses an interesting topic for future research.

Our study strengthens the evidence regarding the short-term safety of the booster BNT162b2 vaccine in several ways. First, reports of local and systemic reactions after the third dose were similar to those observed after the second dose, which was shown in clinical trials to be safe (*26*). Second, the considerable changes observed for all indicators during the first 2 days after receiving the third vaccine, including self-reported reactions and well-being indicators, as wells as objective physiologic indicators collected by the smartwatch, returned to their baseline levels. Third, regardless of the observed differences between subpopulations, our analyses indicated a clear pattern of return to baseline levels in all considered subpopulations. Fourth, we observed no change in SpO_2 compared with baseline levels, indicating that major adverse health consequences are less likely.

In conclusion, our study supports the short-term safety of the third BNT162b2 mRNA COVID-19 (booster) vaccine dose and mitigates, in part, concerns regarding its short-term effects. The medical and scientific communities could greatly benefit from the largely unbiased data generated by digital health technologies, such as the wearable devices that we analyzed in this study. Our findings could also be of interest to public health officials and other stakeholders because it is essential that objective measures are given attention in the critical evaluation of clinical trials.

Researchers interested in obtaining an aggregated version of the data and statistical code sufficient to reproduce the results reported in this article should contact the corresponding author (Erez Shmueli, shmueli@tau.ac.il)..

D.Y. and E.S. designed the study; M.M., T.P., S.G., and E.S. collected and assembled data; M.M., G.G., M.L.B., D.Y., and E. S. analyzed and interpreted data; M.M., D.Y., and E.S. performed statistical analysis; M.M., M.Y., D.Y., and E.S. wrote a draft of the article; D.Y. and E.S. critically revised the article and obtained funding for the study, and all authors approved the final version of the article.

About the Author

Mrs. Mofaz is a doctoral candidate in the Industrial Engineering Department at Tel Aviv University, Tel Aviv, Israel. Her primary research interests are personalized medicine and early detection of diseases using machine learning tools.

References

1. Kupferschmidt K, Wadman M. Delta variant triggers new phase in the pandemic. Science. 2021;372:1375–6. https://doi.org/10.1126/science.372.6549.1375
2. World Health Organization. Tracking SARS-CoV-2 variants [cited 2022 Apr 13]. https://www.who.int/en/activities/tracking-SARS-CoV-2-variants
3. Mlcochova P, Kemp SA, Dhar MS, Papa G, Meng B, Ferreira IA, et al.; Indian SARS-CoV-2 Genomics Consortium (INSACOG); Genotype to Phenotype Japan (G2P-Japan) Consortium; CITIID-NIHR BioResource COVID-19 Collaboration. SARS-CoV-2 B.1.617.2 Delta variant replication and immune evasion. Nature. 2021;599:114–9. https://doi.org/10.1038/s41586-021-03944-y
4. Centers for Disease Control and Prevention. Delta variant: what we know about the science [cited 2022 Apr 13]. https://stacks.cdc.gov/view/cdc/108671
5. Mahase E. Delta variant: what is happening with transmission, hospital admissions, and restrictions? BMJ. 2021;373:n1513. https://doi.org/10.1136/bmj.n1513
6. World Health Organization. Weekly epidemiological update on COVID-19, August 17, 2021 [cited 2022 Apr 13]. https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---17-august-2021
7. Wadman M. Israel's grim warning: Delta can overwhelm shots. Science. 2021;373:838–9. https://doi.org/10.1126/science.373.6557.838
8. Munitz A, Yechezkel M, Dickstein Y, Yamin D, Gerlic M. BNT162b2 vaccination effectively prevents the rapid rise of SARS-CoV-2 variant B.1.1.7 in high-risk populations in Israel. Cell Rep Med. 2021;2:100264. https://doi.org/10.1016/j.xcrm.2021.100264
9. Lopez Bernal J, Andrews N, Gower C, Gallagher E, Simmons R, Thelwall S, et al. Effectiveness of COVID-19 vaccines against the B.1.617.2 (Delta) variant. N Engl J Med. 2021;385:585–94. https://doi.org/10.1056/NEJMoa2108891
10. Pouwels KB, Pritchard E, Matthews PC, Stoesser N, Eyre DW, Vihta K-D, et al. Effect of Delta variant on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK. Nat Med. 2021;27:2127–35. https://doi.org/10.1038/s41591-021-01548-7
11. Sheikh A, McMenamin J, Taylor B, Robertson C; Public Health Scotland and the EAVE II Collaborators. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. Lancet. 2021;397:2461–2. https://doi.org/10.1016/S0140-6736(21)01358-1
12. Nasreen S, He S, Chung H, Brown KA, Gubbay JB, Buchan SA, et al. Effectiveness of COVID-19 vaccines against variants of concern in Ontario. Nat Microbiol. 2022;7:379–85. https://doi.org/10.1038/s41564-021-01053-0
13. Centers for Disease Control and Prevention. COVID-19 datasets—government data. [cited 2022 Apr 13]. https://data.cdc.gov/browse?q=covid-19
14. Ministry of Health. The Ministry of Health Director General has approved the recommendation to administer a third vaccine dose to 50-year-olds and older and to other population [cited 2022 Apr 13]. https://www.gov.il/en/departments/news/13082021-01
15. Ministry of Health. The Vaccination Advisory Committee presented data and recommended the administration of a third dose to older adults [cited 2022 Apr 13]. https://www.gov.il/en/departments/news/29072021-04
16. Prime Minister's Office. Statement by PM Bennett on third dose of the COVID vaccine to Israeli citizens over the age of 60 [cited 2022 Apr 13]. https://www.gov.il/en/Departments/news/event_press29071
17. Ministry of Health. The vaccination policy and the new green pass that will take effect soon [cited 2022 Apr 13]. https://www.gov.il/en/departments/news/29082021-01
18. Centers for Disease Control and Prevention. Joint statement from HHS public health and medical experts on COVID-19 booster shots. CDC online newsroom [2022 Apr 13]. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/booster-shot.html?s_cid=11709:covid%20vaccine%20booster:sem.ga:p:RG:GM:gen:PTN.Grants:FY22
19. Centers for Disease Control and Prevention. COVID-19 vaccines for people who are moderately to severely immunocompromised [cited 2022 Apr 13]. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html?s_cid=10483:immunocompromised%20and%20covid%20vaccine:sem.ga:p: :GM:gen:PTN:FY21
20. US Food and Drug Administration. Joint statement from HHS public health and medical experts on COVID-19 booster shots [2022 Apr 13]. https://www.hhs.gov/about/news/2021/08/18/joint-statement-hhs-public-health-and-medical-experts-covid-19-booster-shots.html
21. Kamar N, Abravanel F, Marion O, Couat C, Izopet J, Del Bello A. Three doses of an mRNA Covid-19 vaccine in solid-organ transplant recipients. N Engl J Med. 2021;385:661–2. https://doi.org/10.1056/NEJMc2108861
22. Food and Drug Administration. Development and licensure of vaccines to prevent COVID-19 [cited 2022 Apr 13]. https://www.fda.gov/media/139638/download
23. Gepner Y, Mofaz M, Oved S, Yechezkel M, Constantini K, Goldstein N, et al. Utilizing wearable sensors for continuous and highly-sensitive monitoring of reactions to the BNT162b2 mRNA COVID-19 vaccine. Commun Med. 2022;2:1–8.
24. Hajduczok AG, DiJoseph KM, Bent B, Thorp AK, Mullholand JB, MacKay SA, et al. Physiologic response to the Pfizer-BioNTech COVID-19 vaccine measured using wearable devices: prospective observational study. JMIR Form Res. 2021;5:e28568. https://doi.org/10.2196/28568
25. Oved S, Mofaz M, Lan A, Einat H, Kronfeld-Schor N, Yamin D, et al. Differential effects of COVID-19 lockdowns on well-being: interaction between age, gender and chronotype. J R Soc Interface. 2021;18:20210078. https://doi.org/10.1098/rsif.2021.0078

26. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al.; C4591001 Clinical Trial Group. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. N Engl J Med. 2020;383:2603–15. https://doi.org/10.1056/NEJMoa2034577

27. Garmin. VÍVOSMART® 4 owner's manual. 2018 [cited 2022 Apr 13]. https://www8.garmin.com/manuals/webhelp/vivosmart4/EN-US/vivosmart_4_OM_EN-US.pdf

28. Garmin. What is the stress level feature on my Garmin watch? [cited 2022 Apr 13]. https://support.garmin.com

29. Kim H-G, Cheon E-J, Bai D-S, Lee YH, Koo B-H. Stress and heart rate variability: a meta-analysis and review of the literature. Psychiatry Investig. 2018;15:235–45. https://doi.org/10.30773/pi.2017.08.17

30. Pereira T, Almeida PR, Cunha JP, Aguiar A. Heart rate variability metrics for fine-grained stress level assessment. Comput Methods Programs Biomed. 2017;148:71–80. https://doi.org/10.1016/j.cmpb.2017.06.018

31. Reddy RK, Pooni R, Zaharieva DP, Senf B, El Youssef J, Dassau E, et al. Accuracy of wrist-worn activity monitors during common daily physical activities and types of structured exercise: evaluation study. JMIR Mhealth Uhealth. 2018;6:e10338. https://doi.org/10.2196/10338

32. Bent B, Goldstein BA, Kibbe WA, Dunn JP. Investigating sources of inaccuracy in wearable optical heart rate sensors. NPJ Digit Med. 2020;3:18. https://doi.org/10.1038/s41746-020-0226-6

33. Garmin. Accuracy [cited 2022 Apr 13]. https://support.garmin.com/enUS/?faq=aZc8RezeAb9LjCDpJplTY7#:~:text=Garmin%C2%AE%20GPS%20receivers%20are,to%20its%20Satellite%20Information%20Page

34. Derrick B, Dobson-Mckittrick A, Toher D, White P. Test statistics for comparing two proportions with partially overlapping samples. J Appl Quant Methods. 2015;10:1–14.

35. Derrick B, Russ B, Toher D, White P. Test statistics for the comparison of means for two samples that include both paired and independent observations. J Mod Appl Stat Methods. 2017;16:9. https://doi.org/10.22237/jmasm/1493597280

36. Bunders MJ, Altfeld M. Implications of sex differences in immunity for SARS-CoV-2 pathogenesis and design of therapeutic interventions. Immunity. 2020;53:487–95. https://doi.org/10.1016/j.immuni.2020.08.003

37. Menni C, Klaser K, May A, Polidori L, Capdevila J, Louca P, et al. Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID Symptom Study app in the UK: a prospective observational study. Lancet Infect Dis. 2021;21:939–49. https://doi.org/10.1016/S1473-3099(21)00224-3

38. European Medicines Agency. Clinical trials in human medicines [cited 2022 Apr 13]. https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials-human-medicines

39. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al.; COVE Study Group. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2021;384:403–16. https://doi.org/10.1056/NEJMoa2035389

40. Voysey M, Clemens SA, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al.; Oxford COVID Vaccine Trial Group. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet. 2021;397:99–111. https://doi.org/10.1016/S0140-6736(20)32661-1

Address for correspondence: Erez Shmueli, Department of Industrial Engineering, Tel Aviv University, 30 Chaim Levanon St, Tel Aviv 6997801, Israel; email: shmueli@tau.ac.il
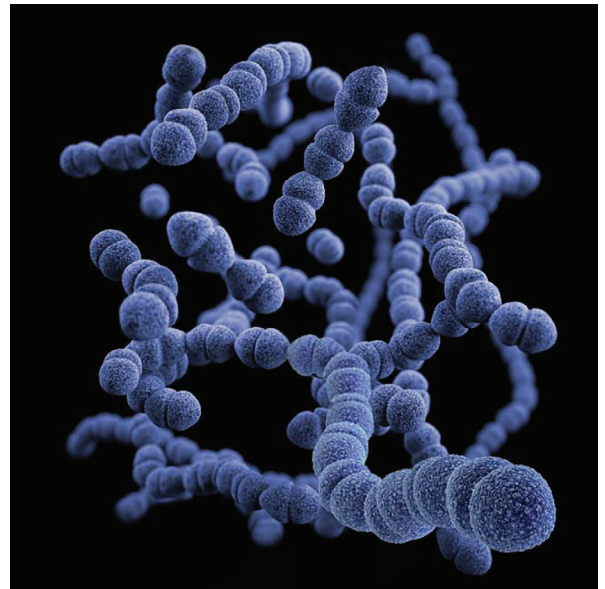
Self-Reported and Physiologic Reactions to Third BNT162b2 mRNA COVID-19 (Booster) Vaccine Dose

Appendix Part A: Study Protocol

Background

Vaccination is widely accepted as the most prominent measure in the fight against COVID-19, posing the greatest hope for ending this major global health pandemic and related economic crisis (*1*). Consequently, an unprecedented international effort by private and public institutions alike was directed at accelerating the traditionally lengthy vaccine-development process (*2–4*).

On 2 December 2020, less than a year from the pandemic outbreak, the first vaccine, BNT162b2 mRNA (Pfizer-BioNTech), was granted an Emergency Use Authorization (EUA) by the UK Medicines and Healthcare Products Regulatory Agency (MHRA) (*5*). This initial authorization was followed by rapid authorizations for emergency use in several countries, with the U.S. Food and Drug Administration (FDA) among the first to do so (*6*).

Safety data from a randomized controlled trial suggests a favorable safety profile for the BNT162b2 vaccine (*7*). Specifically, the local and systemic self-reported reactions during the first 7 days after vaccination were mainly mild to moderate, with a median onset of 0–2 days after vaccine administration and a median duration of 1–2 days. The most frequently reported reactions were fatigue, headache, muscle pain, chills, joint pain, and fever (*7*). The incidence of serious adverse events was low and was similar between vaccine- and placebo-treated participants. The safety of the new vaccine over a median of 2 months post-vaccination was similar to that of other viral vaccines. A considerable fraction of the participants did not report any reaction or adverse event. Likewise, several other vaccine candidates, including ChAdOx1 nCoV-19 (Oxford/AstraZeneca) and

mRNA-1273 (Moderna), received EUAs following similar encouraging safety results by randomized controlled trials (*8–10*).

The SARS-CoV-2 Delta variant (also termed variant B.1.617.2) was discovered in October 2020, in India, and was designated as a variant of concern by the World Health Organization (WHO) in May 2021 (*11–13*). The rapid increase in hospitalizations in Israel associated with the Delta-driven COVID-19 resurgence, and the imminent risk for hospital overcrowding, led the Israeli government to initialize on July 30, 2021, an unparalleled, pro-active, national third (booster) vaccine shot campaign, offering the BNT162b2 mRNA COVID-19 vaccine to persons over the age of 60. On August 13, 2021, the booster campaign was expanded to include those over 50 years of age, reaching 63% third-dose coverage among the eligible population within only 26 days (*14–17*). Two weeks later, on August 29, 2021, the campaign was expanded to include all persons 16+ of age, demanding only that 5 months have passed since the receipt of the second dose, reaching 40% third-dose coverage among the eligible population under 50 years of age, within 16 days (*18,19*).

Currently, limited information is available on the safety of a BNT162b2 third dose (*20,21*), with such a booster vaccine yet to be authorized by the U.S. Food and Drug Administration (FDA) to the general population (*22*). While recent evidence shows that a third BNT162b2 dose in immunocompromised persons has a favorable safety profile (*21,23*), the safety of a third (booster) dose in the general population has not yet been fully established.

Methods

Study Design

In this study we will analyze data that was already collected and will be collected as part of the PerMed study (*24*). Participants in the PerMed study are recruited for a period of 2 years, during which they are equipped with a Garmin Vivosmart 4 smartwatches and are asked to wear them as much as they could. In addition, participants install 2 applications on their mobile phones: an application that passively collects data from the smartwatch and a dedicated mobile application that enables participants to fill a

daily questionnaire and to report their vaccine date and specific hour. In this study, we will consider for each participant, the 7-days period before any vaccination dose as the baseline period.

Participants

The inclusion criteria for the PerMed study includes those aged >18 years. Persons who are not eligible to give and sign a consent form of their free are excluded. In this study, we will analyze the data of participants aged 18 years and above, who reported receiving at least 1 dose of the BNT162b2 mRNA COVID-19 vaccine after joining the PerMed study. To recruit participants and ensure they complete all the study's requirements, we will hire a professional survey company. Potential participants will be recruited through advertisements in social media, online banners, and word-of-mouth. The survey company is responsible for guaranteeing the participants meet the study's requirements, in particular, that the questionnaires are filled daily, ensuring the smartwatches are charged constantly and worn properly, and assisting participants resolve technical problems.

Study Procedures

Before participation in the study, all participants will be advised orally and in writing about the nature of the experiments and give written, informed consent. At this time, participants will be asked to complete an enrollment questionnaire that includes demographic information and health status. In addition, participants will be asked to install 2 applications on their mobile phones: an application that passively collects data from the smartwatch and the PerMed application, which enables participants to fill in the daily questionnaires. Participants will be given instructions regarding the self-reported symptoms questionnaires and how to operate the smartwatch, which they will wear as much as they can.

Enrollment Questionnaire

All participants will fill a 1-time enrollment questionnaire that includes demographic questions and questions about the participant's health condition in general. Specifically, the questionnaire will include the following: age, sex, height, weight and underlying medical conditions (Listed in Table 1, main text). Other questions such as

name, address, phone and email will be recorded and used by the survey company to contact the participants. The answers will be filled-in directly by the survey company to the study's secured dashboard.

Monitoring Device

Participants will be equipped with Garmin Vivosmart 4 smart fitness trackers. Among other features, the smartwatch provides all-day heart rate and heart rate variability and during-night blood oxygen saturation level tracking capabilities (*25*).

The optical wrist heart rate (HR) monitor of the smartwatch is designed to continuously monitor a user's heart rate. The frequency at which heart rate is measured varies and may depend on the level of activity of the user: when the user starts an activity, the optical HR monitor's measurement frequency increases.

Since heart rate variability (HRV) is not easily accessible through Garmin's application programming interface (API), we use Garmin's stress level instead, which is calculated based on HRV. Specifically, the device uses heart rate data to determine the interval between each heartbeat. The variable length of time between each heartbeat is regulated by the body's autonomic nervous system. Less variability between beats correlates with higher stress levels, whereas an increase in variability indicates less stress (*26*). A similar relationship between HRV and stress was also seen in (*27,28*).

The Pulse Ox monitor of the smartwatch uses a combination of red and infrared lights with sensors on the back of the device to estimate the percentage of oxygenated blood (peripheral oxygen saturation). The Pulse Ox monitor is activated each day at a fixed time for a period of 4 hours (the default is 2:00 AM–6:00 AM).

Examining the data collected in our study, we identified an HR sample roughly every 15 seconds, an HRV sample every 180 seconds, and an blood oxygen saturation level sample every 60 seconds.

While the Garmin smartwatch provides state-of-the-art wrist monitoring, it is not a medical-grade device, and some readings may be inaccurate under certain circumstances, depending on factors such as the fit of the device and the type and intensity of the activity undertaken by a participant (*29–31*).

Vaccination Questionnaire

The vaccination questionnaire we will use includes the following question:

COVID-19 vaccination – date, time, and dose number.

Daily Questionnaires

All participants will complete the daily self-reported questionnaire in a dedicated application (the PerMed mobile application). The daily questionnaire we will use includes the following questions:

How is your mood today? • Awful (−2)• Bad (−1)• OK (0)• Good (1)• Excellent (2)

How would you describe the level of your stress during the last day?• Very Low (−2)• Low (−1)• Medium (0)• High (1)• Very high (2)

How would you define your last night sleep quality?
• Awful (−2)
• Bad (−1)
• OK (0)
• Good (1)
• Excellent (2)

Try to remember how many minutes of sports activity you performed on the last day?

Have you experienced one or more of the following symptoms in the last 24 hours?
• My general feeling is good, and I have no symptoms
• Heat measured above 37.5
• Cough
• Sore throat
• Runny nose
• Headache
• Shortness of breath
• Muscle aches
• Weakness / fatigue
• Diarrhea
• Nausea / vomiting
• Chills
• Confusion
• Loss of sense of taste / smell
• Another symptom.

Data Storage

Data collected from the mobile phone application and from the smartwatches will be stored on a secure server within Tel Aviv University facilities. The server runs a CentOS operating system and is located in Software Engineering Building at Tel Aviv University. This server is protected behind the university's firewall and is not connected to external networks. In addition, a secure connection through an SSL protocol and a

trusted certificate will be obtained for the transfer of information from the mobile phone application into the secured server.

Access will be restricted to investigators in the study. The information from the mobile application will be stored in a structured manner on the secured server without any explicitly identifying information (name, ID number, email). Each participant will be assigned a coded participant number that will be used to identify the subject in the database. The code with the identified information will be stored in an encrypted form on a separate secured server that only the research manager will have access to. Access to all servers is restricted with username and password.

All (non-digital) questionnaires and signed informed consent documents will be stored in a secured cabinet in Tel Aviv University, to which only the research manager and the principal investigators will have access. No data collected as part of the study will be added to persons' medical charts.

Data Processing

We will perform several preprocessing steps. Concerning the daily questionnaires, in cases where participants will fill in the daily questionnaire more than once on a given day, only the last entry for that day will be considered, as it is reasoned that the last one likely best represented the entire day. Self-reported symptoms that are entered as the free text will be manually categorized. With regard to the smartwatch physiologic indicators, data will first be aggregated per hour (by taking the mean value). Then, to impute missing values, we will perform a linear interpolation. Finally, data will be smoothed by calculating the moving average value using a 5-hour sliding window.

Data Analysis

For each participant, we defined the 7-day period before vaccination as a baseline. First, for the period of 48 hours from vaccination, we will calculate the percentage of participants who reported new local or systemic reactions compared with their baseline period (i.e., the last questionnaire each participant filled during the baseline period). For each reaction, a 90% confidence interval will be calculated, assuming a β distribution, with parameter α corresponding to the number of participants reporting that reaction plus one (i.e., "successes"), and parameter β corresponding to the number of participants who

did not report that reaction plus one (i.e., "failures"). To determine the statistical significance of differences between the first and third doses and between the second and third doses as reflected by the extent of reported reactions, we will use a 2-proportion Z-test.

Next, we will calculate the changes in well-being indicators reported post-vaccination compared with those reported during the baseline period. Specifically, for each indicator and each participant, we will calculate the difference between the value in each of the 3 days post-vaccination and the corresponding value in the baseline period (i.e., the last questionnaire filled during the baseline period). Then, for each indicator and each of the 3 days post vaccination, we will calculate the mean difference value over all participants and the associated 90% confidence interval.

Finally, we will compare the changes in smartwatch physiologic indicators over the 7 days (168 hours) post vaccination with those of the baseline period. To do so, we will perform the following steps. First, for each participant and each hour during the 7 days post vaccination, we will calculate the difference between that hour's indicator value and that of the corresponding hour in the baseline period (keeping the same day of the week and same hour during the day). Then, we will calculate the mean difference value for each hour over all participants, as well as the 90% confidence interval, corresponding to a significance level of 0.05 in a 1-sided t-test. To determine the statistical significance of differences between the first and third doses and between the second and third doses as reflected by changes in smartwatch indicators during the 48 hours post-vaccination, we will use a 2-sample t-test with unequal variance.

Potential Risks and Risk Management

No specific risks arising from the smartwatches are expected, as the device is already commercialized with no known adverse reactions. The main risk in this study is the leakage of private data which we intend to manage as we describe in the following section.

Privacy/Confidentiality

Results from this study will be handled at an aggregated level. Individual data records will remain confidential and will not be published or shared with any third party.

Signed and dated informed consent forms, as well as data recording sheets (e.g., case report forms) will be stored in locked cabinets during the study and following its completion. A file containing the personal details of the participants will be coded to help preserve confidentiality and will be separated from all other data collected throughout the study. This file will be kept by the principal investigator. Data will be stored on computers in password-protected files.

The data obtained from the smartwatch used in this study will be linked to a coded participant number. The smartwatch does not include a global positioning system. Data collected by the PerMed application will arrive directly to PerMed back-end servers and will be stored securely.

Appendix Part B: Additional Results

Changes in Objective Physiologic Indicators Measured through the Smartwatch following the Three Vaccine Doses

Changes in objective physiologic indicators observed during the first 2 days after the second and third vaccine doses are similar, and considerably greater than those observed following the first dose.
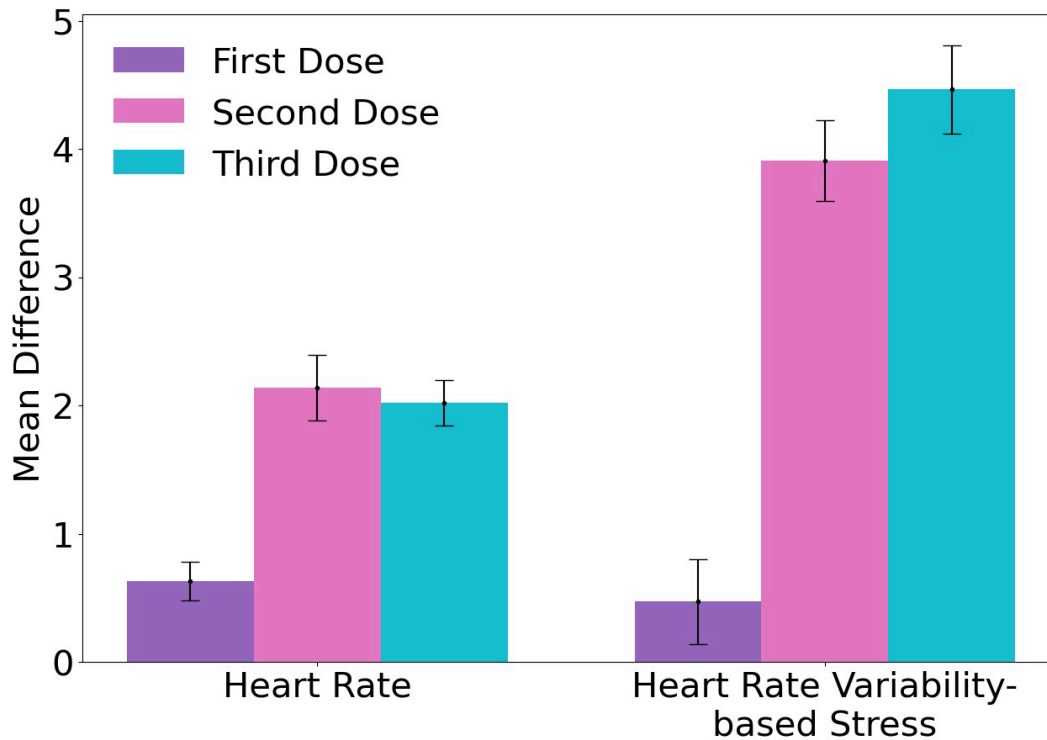
Appendix Figure 1. Changes in objective physiologic indicators measured through the smartwatch during the first 2 days after vaccine. Mean difference in smartwatch-recorded heart rate and heart rate variability-based following the first, second and third dose, compared with their baseline levels. Changes in objective physiologic indicators were calculated by subtracting the baseline values from the mean value of the first 2 days following the vaccine dose. Error bars represent 90% confidence intervals.

Changes in reported well-being indicators – stratification by age group

Changes in well-being observed during the first 2 days after the third vaccine dose were found to be higher for participants younger than 50 years compared with those between 50 and 65 years, and consequently higher than those older than 65 years, with the exception of reported stress level (Appendix Figure 2).
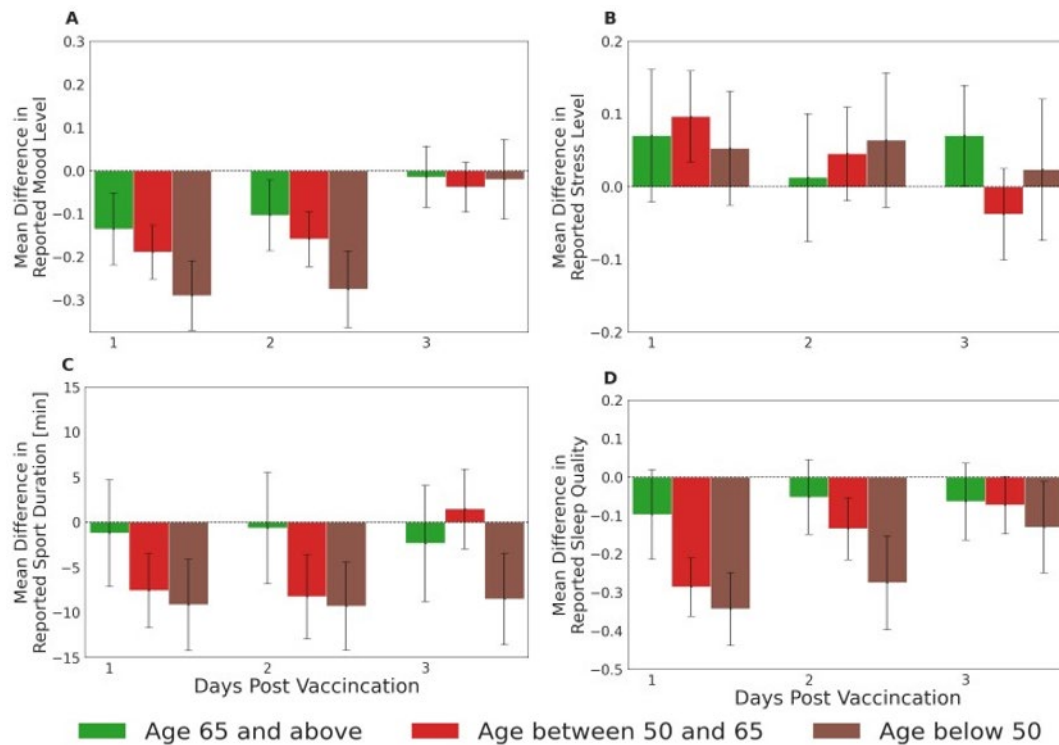
Appendix Figure 2. Changes in well-being indicators reported by participants through the mobile application stratified by age group. (A) mood level, measured on a 1-to-5 Likert scale. (B) Stress level, measured on a 1-to-5 Likert scale. (C) Sport duration, measured in minutes. (D) Sleep quality, measured on a 1-to-5 Likert scale. Changes in well-being indicators were calculated by subtracting the baseline values from the daily values. Error bars represent 90% confidence intervals. Horizontal dashed lines represent no change compared with baseline levels.

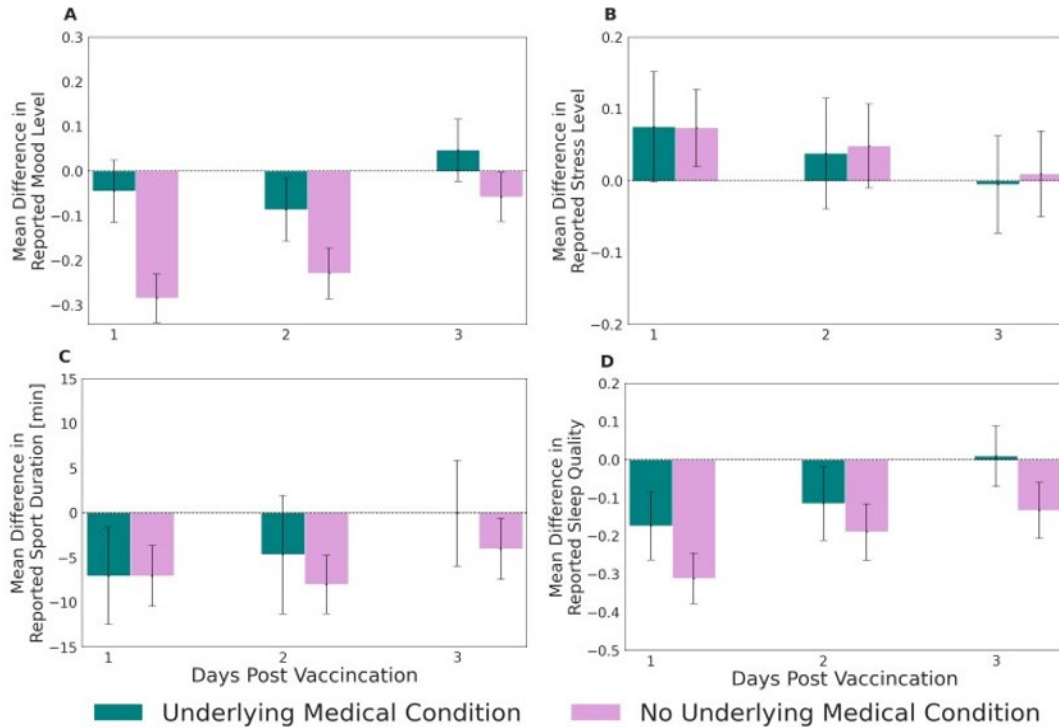**Changes in Reported Well-Being Indicators – Stratification by Sex**

Changes in well-being observed during the first 2 days after the third vaccine dose were found to be similar for males and females (Appendix Figure 3).
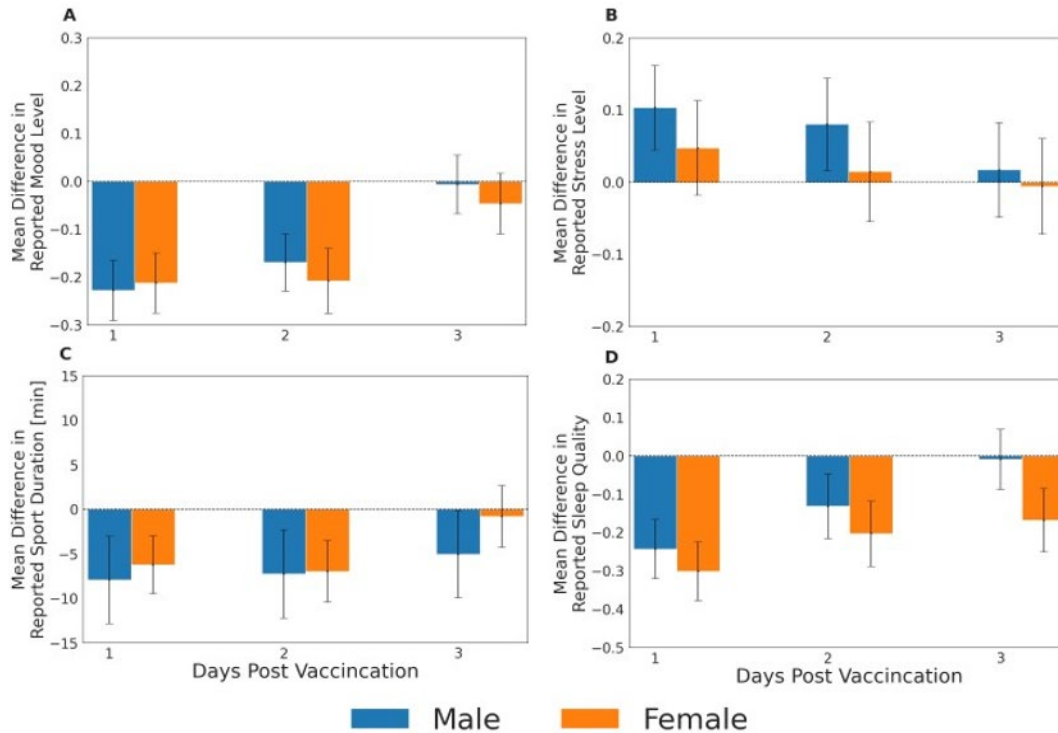
Appendix Figure 3. Changes in well-being indicators reported by participants through the mobile application stratified by sex. (A) mood level, measured on a 1-to-5 Likert scale. (B) Stress level, measured on a 1-to-5 Likert scale. (C) Sport duration, measured in minutes. (D) Sleep quality, measured on a 1-to-5 Likert scale. Changes in well-being indicators were calculated by subtracting the baseline values from the daily values. Error bars represent 90% confidence intervals. Horizontal dashed lines represent no change compared with baseline levels.

Changes in reported well-being indicators – stratification by underlying medical condition

Changes in mood level and sleep quality observed during the first 2 days after the third vaccine dose were found to be higher for participants without underlying medical conditions compared with those with underlying medical condition (Appendix Figure 4).

Appendix Figure 4. Changes in well-being indicators reported by participants through the mobile application stratified by underlying medical conditions. (A) mood level, measured on a 1-to-5 Likert scale. (B) Stress level, measured on a 1-to-5 Likert scale. (C) Sport duration, measured in minutes. (D) Sleep quality, measured on a 1-to-5 Likert scale. Changes in well-being indicators were calculated by subtracting the baseline values from the daily values. Error bars represent 90% confidence intervals. Horizontal dashed lines represent no change compared with baseline levels.

Changes in Physiologic Indicators – Stratification by Age Group
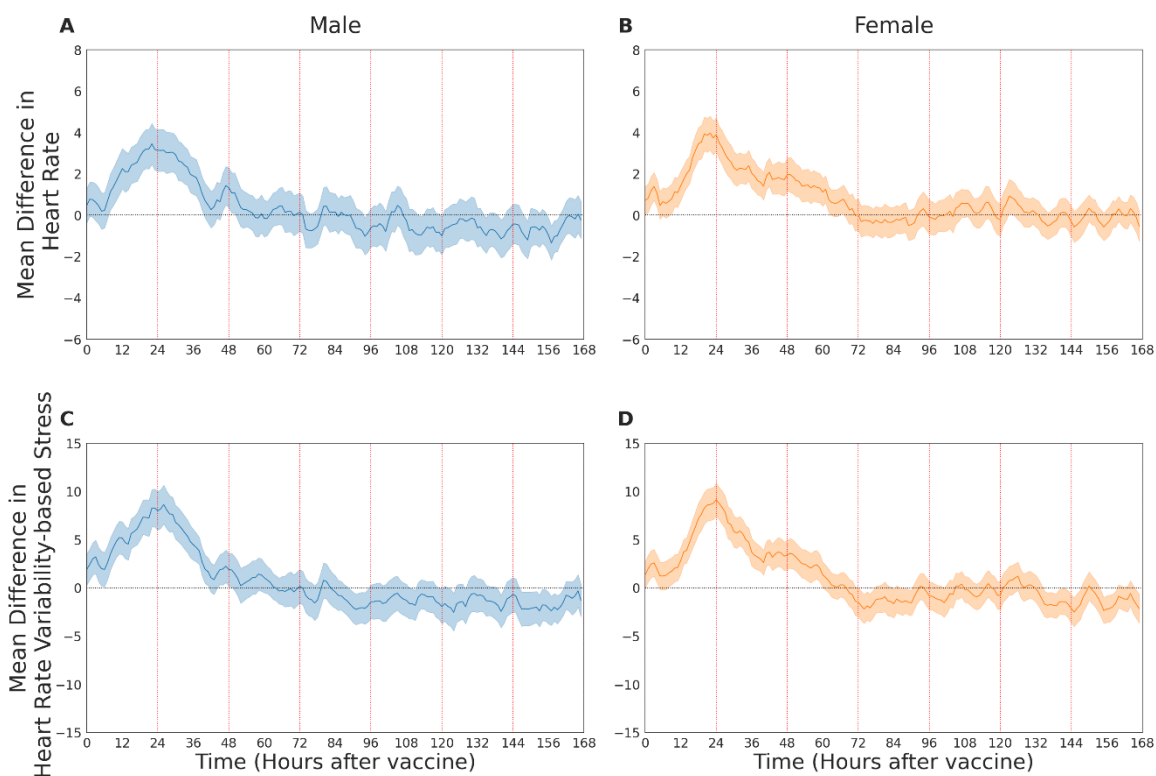
Changes in physiologic indicators after the third vaccine dose stratified by age group were consistent with those observed in the general population (considerable changes during the first 2 days after vaccine administration that faded nearly entirely after 3 days). These changes were found to be higher for participants younger than 50 years compared with those between 50 and 65 years, and consequently higher than those older than 65 years (Appendix Figure 5).
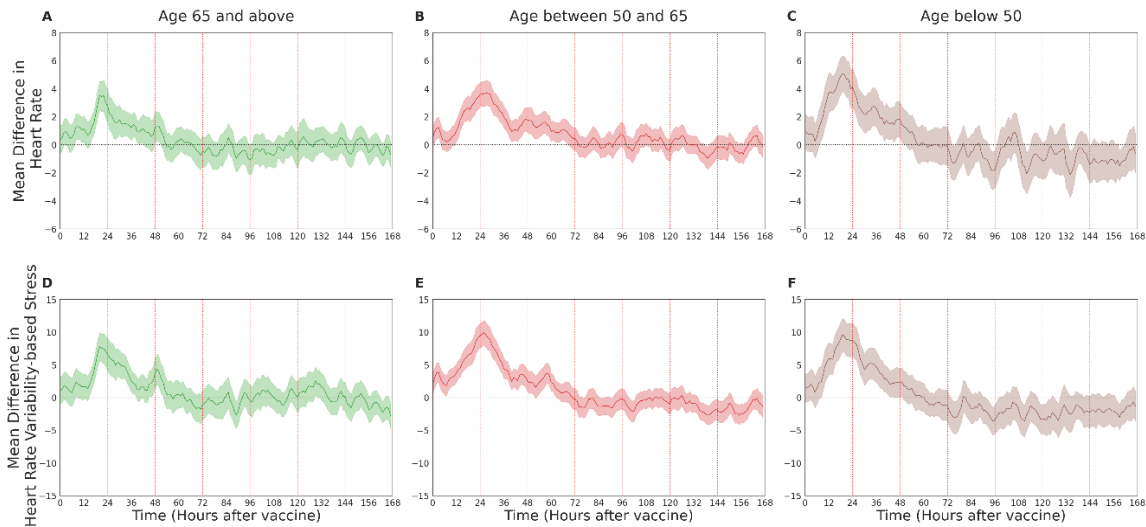
Appendix Figure 5. Changes in physiologic indicators measured through the smartwatch stratified by age groups. Mean difference in heart rate and heart rate variability-based stress indicators following the third dose, recorded by a smartwatch, compared with their baseline levels: (**A** and **B**) heart rate, (**C** and **D**) heart rate variability-based stress. Mean values are depicted as solid lines; 90% confidence intervals are presented as shaded regions. The horizontal dashed line represents no change compared with the baseline levels, and vertical lines represent 24-hour periods.

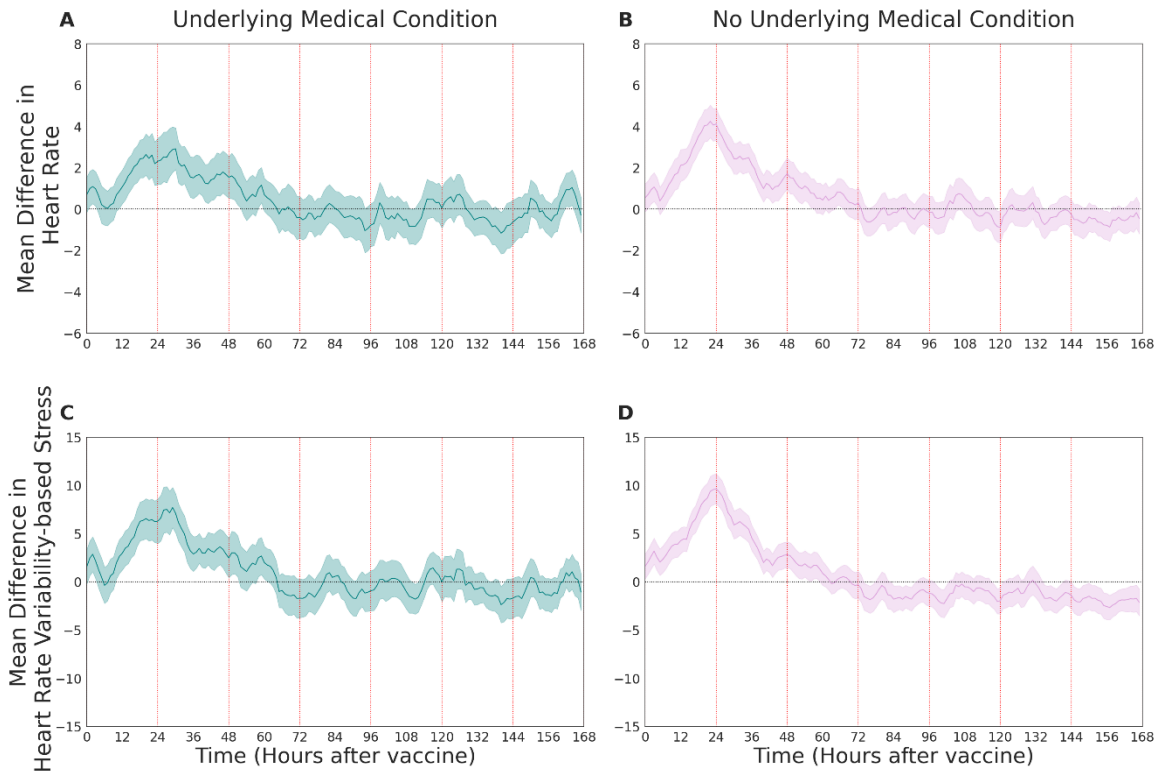**Changes in Physiologic Indicators – Stratification by Sex**

Changes in physiologic indicators after the third vaccine dose stratified by sex were consistent with those observed in the general population (considerable changes during the first 2 days after vaccine administration that faded nearly entirely after 3 days). These changes were found to be higher for females compared with males (Appendix Figure 6).

Appendix Figure 6. Changes in physiologic indicators measured through the smartwatch stratified by sex. Mean difference in heart rate and heart rate variability-based stress indicators following the third dose, recorded by a smartwatch, compared with their baseline levels: (**A** and **B**) heart rate, (**C** and **D**) heart rate variability-based stress. Mean values are depicted as solid lines; 90% confidence intervals are presented as shaded regions. The horizontal dashed line represents no change compared with the baseline levels, and vertical lines represent 24-hour periods.

**Changes in Physiologic Indicators – Stratification by Underlying Medical Condition**

Changes in physiologic indicators after the third vaccine dose stratified by underlying medical condition were consistent with those observed in the general population (considerable changes during the first 2 days after vaccine administration that faded nearly entirely after 3 days). These changes were found to be higher for participants without underlying medical conditions compared with those with underlying medical condition (Appendix Figure 7).

Appendix Figure 7. Changes in physiologic indicators measured through the smartwatch stratified by underlying medical conditions. Mean difference in heart rate and heart rate variability-based stress indicators following the third dose, recorded by a smartwatch, compared with their baseline levels: (A and B) heart rate and (C and D) heart rate variability-based stress. Mean values are depicted as solid lines; 90% confidence intervals are presented as shaded regions. The horizontal dashed line represents no change compared with the baseline levels, and vertical lines represent 24-hour periods.

Thirty Days Analysis for Self-Reported Local and Systemic Reactions after the Third Dose

We observe a sharp decline in reported local and systemic reactions following 3 days after the third vaccination dose, and nearly a complete halt within 30 days post-vaccination (Appendix Figure 8). Fatigue and headache were the most frequent reactions reported and lasted longer than the other reported reactions.
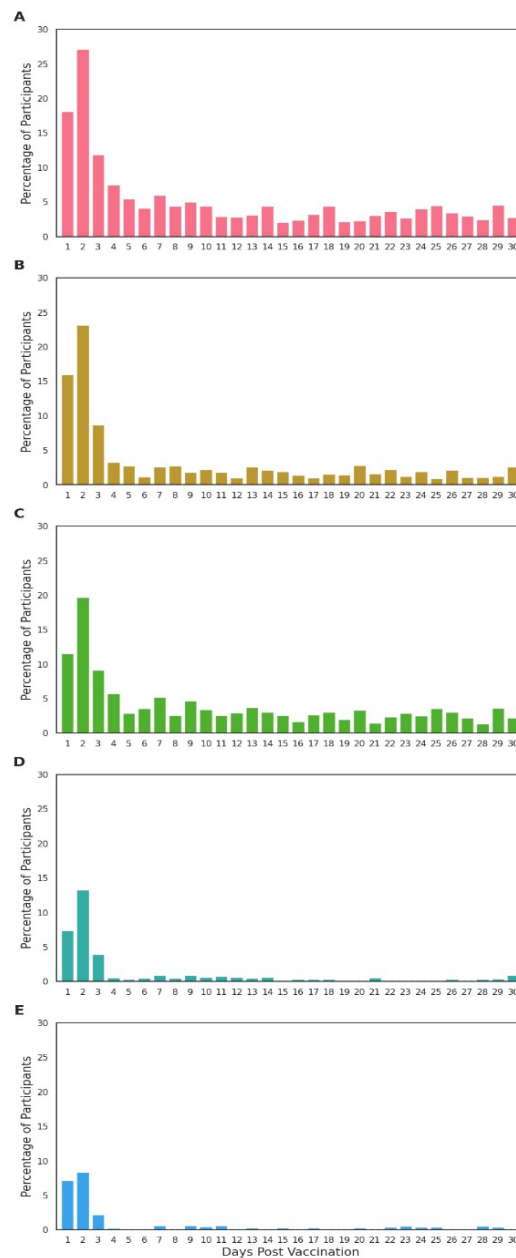
Appendix Figure 8. Most frequent local and systemic reactions reported by participants through the mobile application after the third dose. (A) fatigue, (B) muscle pain, (C) headache, (D) fever, and (E) chills.

Pairwise Analysis of Doses

A considerable number of participants joined our study after receiving the first or second dose. Thus, in our main analyses, we compared the third dose to the first or second dose by using statistical significance tests for comparing the means of 2 partially overlapping samples with unequal variance. To further support the results of our main analyses, we also conducted an analysis where we examined changes in reactions for the subgroups of participants who reported receiving all 3 doses. To determine the statistical significance of differences in the proportions of participants' self-reported reactions between doses, we used McNemar tests (Appendix Table 1). To determine the statistical significance of differences in the change in smartwatch measurements between doses we used paired t-tests (Appendix Table 2).

Appendix Table 1. Self-reported reactions (N = 53)

Compared doses	% participants who reported no reaction after vaccination	p value
First and third	First dose: 84.91%, third dose: 64.51%	<0.001
Second and third	Second dose: 75.47%, third dose: 64.51%	<0.01

Appendix Table 2. Change in smartwatch measurements (N = 69)

Measure	Compared doses	Mean difference in measure in the 48 h postvaccination	p value
Heart rate	First and third	First dose: 0.521, third dose: 2.168	<0.05
	Second and third	Second dose: 1.617, third dose: 2.168	0.405
Heart rate variability	First and third	First dose: 1.298, third dose: 6.204	<0.01
	Second and third	Second dose: 4.343, third dose: 6.204	0.239

Calculation of Required Sample Size

The primary goal of the study was to compare reactions following the third dose to those observed in the first and second doses. Particularly, we wanted to know whether reactions following the third dose will be greater than those observed following the second dose. The logic for this notion is the expectation that reactions following primary exposure are typically milder than those following subsequent exposure (namely second or booster dose). Thus, to determine the required sample size, we first identified the five most prevalent systemic reactions observed during the Pfizer clinical trial: headache, fatigue, fever, chills, and muscle pain. Based on those trials, the frequency of these reactions ranged between 16%–59% in persons 16–55, and 11%–51% in persons >55 (*7*). We considered a standard statistical power of >80% for a scenario where reactions are

more prevalent at least 10% than those observed in the clinical trials. We conservatively assumed a non-repeated framework (i.e., different participants received the third dose than those who received the first and second doses). Taken together, we used a Z-test to evaluate the difference in the two population proportions. Under the standard assumptions of $\alpha = 0.05$, $\beta = 1 - \pi = 0.8$, and the formula $(Z_\alpha + Z_\beta)^2 \times (p_1(1 - p_1) + p_2(1 - p_2))/(p_1 - p_2)^2$, we derived a required n = 203–282 in persons 18–55 (which correspond to 16%–59%) namely >282, and 164–302 (which corresponds to 11%–51%) namely n > 302 in persons >55. To conclude, the actual number of participants in our study is considerably larger than the one required to ensure statistical significance.

The primary goal of the study was to compare reactions following the third dose to those

References

1. World Health Organization. Draft landscape and tracker of COVID-19 candidate vaccines [cited 2022 Apr 13]. https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccine

2. Sharma O, Sultan AA, Ding H, Triggle CR. A review of the progress and challenges of developing a vaccine for COVID-19. Front Immunol. 2020;11:585354. PubMed https://doi.org/10.3389/fimmu.2020.585354

3. Parker EP, Shrotri M, Kampmann B. Keeping track of the SARS-CoV-2 vaccine pipeline. Nat Rev Immunol. 2020;20:650. PubMed https://doi.org/10.1038/s41577-020-00455-1

4. Krammer F. SARS-CoV-2 vaccines in development. Nature. 2020;586:516–27. PubMed https://doi.org/10.1038/s41586-020-2798-3

5. MHRA guidance on coronavirus (COVID-19) - GOV.UK [cited 2022 Apr 13]. https://www.gov.uk/government/collections/mhra-guidance-on-coronavirus-covid-19

6. Food and Drug Administration. FDA takes key action in fight against COVID-19 by issuing emergency use authorization for first COVID-19 vaccine [cited 2022 Apr 13]. https://www.fda.gov/news-events/press-announcements/fda-takes-key-action-fight-against-covid-19-issuing-emergency-use-authorization-first-covid-19

7. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al.; C4591001 Clinical Trial Group. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. N Engl J Med. 2020;383:2603–15. PubMed https://doi.org/10.1056/NEJMoa2034577

8. World Health Organization. Background document on mRNA vaccine BNT162b2 (Pfizer-BioNTech) against COVID-19 [cited 2022 Apr 13]. https://www.who.int/publications/i/item/background-document-on-mrna-vaccine-bnt162b2-(pfizer-biontech)-against-covid-19

9. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al.; COVE Study Group. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2021;384:403–16. PubMed https://doi.org/10.1056/NEJMoa2035389

10. Voysey M, Clemens SA, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al.; Oxford COVID Vaccine Trial Group. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet. 2021;397:99–111. PubMed https://doi.org/10.1016/S0140-6736(20)32661-1

11. Kupferschmidt K, Wadman M. Delta variant triggers new phase in the pandemic. Science. 2021;372:1375–6. https://doi.org/10.1126/science.372.6549.1375

12. World Health Organization. Tracking SARS-CoV-2 variants [cited 2022 Apr 13]. https://www.who.int/en/activities/tracking-SARS-CoV-2-variants

13. Mlcochova P, Kemp SA, Dhar MS, Papa G, Meng B, Ferreira IA, et al.; Indian SARS-CoV-2 Genomics Consortium (INSACOG); Genotype to Phenotype Japan (G2P-Japan) Consortium; CITIID-NIHR BioResource COVID-19 Collaboration. SARS-CoV-2 B.1.617.2 Delta variant replication and immune evasion. Nature. 2021;599:114–9. PubMed https://doi.org/10.1038/s41586-021-03944-y

14. Ministry of Health. The Ministry of Health Director General Has Approved the Recommendation to Administer a Third Vaccine Dose to 50-Year-Olds and Older and to Other Populations | Ministry of Health [cited 2022Apr 13]. https://www.gov.il/en/departments/news/13082021-01

15. Ministry of Health. The Vaccination Advisory Committee Presented Data and Recommended the Administration of a Third Dose to Older Adults [cited 2022Apr 13]. https://www.gov.il/en/departments/news/29072021-04

16. Prime Minister's Office. Statement by PM Bennett on Third Dose of the COVID Vaccine to Israeli Citizens over the Age of 60 [cited 2022 Apr 13]. https://www.gov.il/en/Departments/news/event_press29071

17. Wadman M. Israel's grim warning: Delta can overwhelm shots. Science. 2021;373:838–9. PubMed https://doi.org/10.1126/science.373.6557.838

18. Ministry of Health. The Vaccination Policy and the New Green Pass that will Take Effect Soon [cited 2022 Apr 13]. https://www.gov.il/en/departments/news/29082021-01

19. Centers for Disease Control and Prevention. COVID-19 Datasets- Government Data [cited 2022 Apr 13]. https://data.cdc.gov

20. Centers for Disease Control and Prevention. Joint Statement from HHS Public Health and medical experts on COVID-19 booster shots [2022 Apr 13]. https://www.cdc.gov/media/releases/2021/s0818-covid-19-booster-shots.html

21. Centers for Disease Control and Prevention. COVID-19 Vaccines for Moderately to Severely Immunocompromised People [cited 2022 Apr 13]. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html?s_cid=10483:immunocompromised%20and%20covid%20vaccine:sem.ga:p:RG:GM:gen:PTN:FY21

22. Food and Drug Administration. Joint statement from HHS public health and medical experts on COVID-19 booster shots [cited 2022 Apr 22]. https://www.hhs.gov/about/news/2021/08/18/joint-statement-hhs-public-health-and-medical-experts-covid-19-booster-shots.html

23. Kamar N, Abravanel F, Marion O, Couat C, Izopet J, Del Bello A. Three doses of an mRNA Covid-19 vaccine in solid-organ transplant recipients. N Engl J Med. 2021;385:661–2. PubMed https://doi.org/10.1056/NEJMc2108861

24. Oved S, Mofaz M, Lan A, Einat H, Kronfeld-Schor N, Yamin D, et al. Differential effects of COVID-19 lockdowns on well-being: interaction between age, gender and chronotype. J R Soc Interface. 2021;18:20210078. PubMed https://doi.org/10.1098/rsif.2021.0078

25. Garmin. VÍVOSMART® 4 Owner's Manual. 2018 [cited 2022 Apr 13]. https://www8.garmin.com/manuals/webhelp/vivosmart4/EN-US/vivosmart_4_OM_EN-US.pdf

26. Garmin. What Is the Stress Level Feature on My Garmin Watch? [cited 2022 Apr 13]. https://support.garmin.com

27. Kim H-G, Cheon E-J, Bai D-S, Lee YH, Koo B-H. Stress and heart rate variability: a meta-analysis and review of the literature. Psychiatry Investig. 2018;15:235–45. [PubMed](https://doi.org/10.30773/pi.2017.08.17)

28. Pereira T, Almeida PR, Cunha JP, Aguiar A. Heart rate variability metrics for fine-grained stress level assessment. Comput Methods Programs Biomed. 2017;148:71–80. [PubMed](https://doi.org/10.1016/j.cmpb.2017.06.018)

29. Reddy RK, Pooni R, Zaharieva DP, Senf B, El Youssef J, Dassau E, et al. Accuracy of wrist-worn activity monitors during common daily physical activities and types of structured exercise: evaluation study. JMIR Mhealth Uhealth. 2018;6:e10338. [PubMed](https://doi.org/10.2196/10338)

30. Bent B, Goldstein BA, Kibbe WA, Dunn JP. Investigating sources of inaccuracy in wearable optical heart rate sensors. NPJ Digit Med. 2020;3:18. [PubMed](https://doi.org/10.1038/s41746-020-0226-6)

31. Garmin. Accuracy [cited 2022 Apr 13]. https://www.garmin.com/en-US